

## Remarks

### **The Amendments**

Claim 1 has been amended to recite “[a] chemically modified double stranded short interfering nucleic acid (siNA) molecule comprising a distinct sense strand and an antisense strand wherein: each strand of said siNA molecule is about 18 to about 27 nucleotides in length; the antisense strand of said siNA molecule comprises nucleotide sequence of about 18 to about 27 nucleotides that is complementary to a conserved hepatitis B virus (HBV) RNA comprising SEQ ID NO:16208; the sense strand is complementary to the antisense strand and further comprises a portion of said HBV nucleotide sequence of about 18 to about 27 nucleotides; and about 100% of nucleotides in one or both strands of said siNA are chemically modified.” Support for this claim can be found in the U.S. Provisional patent application No. 60/358,580, incorporated by reference, at, *inter alia*, page 54, line, page 11, and lines 24-28, and throughout the specification.

Dependent claims 2, 9, 11-18 have also been amended to recite the term “siNA” instead of siRNA.

Claim 2 has been amended to recite that the particular siNA molecule is comprised of one or more ribonucleotides. Support for this claim can be found in U.S. Provisional patent application No. 60/358,580 incorporated by reference, at, *inter alia*, page 14, line 20-23 and page 23, line 1-7, and throughout the specification.

Claims 9 and 11-16 have been amended to recite that one or more of the particular recited nucleotides are present in the sense or antisense strand. Support for these claims can be found in U.S. Provisional patent application No. 60/358,580 incorporated by reference, at, *inter alia*, page 11, lines 1-7, and throughout the specification.

Claims 9 and 14 have been amended to recite that one or more of the particular recited nucleotides are 2'-O-methyl purine nucleotides. Support for these claims can be found throughout U.S. Provisional patent application No. 60/358,580 incorporated by reference, at, *inter alia*, page 11, lines 1-6, and in the specification.

Claims 12 and 16 have been amended to recite that one or more of the particular recited nucleotides are 2'-deoxy purine nucleotides. Support for these claims can be found in U.S. Provisional patent application No. 60/358,580 incorporated by reference, at, *inter alia*, page 11, lines 1-6, and throughout the specification.

Claim 13 has been amended to recite that the particular strand includes a terminal phosphorothioate internucleotide linkage at the 3' end of the particular strand. Support for this claim can be found throughout U.S. Provisional patent application No. 60/358,580 incorporated by

reference, at, *inter alia*, page 11, lines 7-30, and throughout the specification.

Claims 11 and 15 have been amended to recite that one or more of the particular recited nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides. Support for these claims can be found in U.S. Provisional patent application No. 60/358,580 incorporated by reference, at, *inter alia* page 11, lines 1-7, and throughout the specification.

Claim 17 has been amended to recite that the particular strand includes a terminal cap moiety at one or both ends of the particular strand. Support for this claim can be found in U.S. Provisional patent application No. 60/358,580 incorporated by reference, at, *inter alia*, page 10, lines 7-12, at page 35, lines 1-15, and throughout the specification.

Claim 18 has been amended to recite that the particular moiety is an inverted deoxy abasic moiety. Support for this claim can be found in U.S. Provisional patent application No. 60/358,580 incorporated by reference, at, *inter alia*, page 13, lines 8-9, page 14, lines 1-4, and throughout the specification.

New claim 25 recites the siNA molecule of claim 1, wherein said antisense strand includes a terminal phosphate group. Support for this claim can be found in U.S. Provisional patent application No. 60/358,580 incorporated by reference, at, *inter alia*, page 16, lines 22-25, and throughout the specification.

New claim 26 recites a composition comprising the siNA molecule of claim 1, in a pharmaceutically acceptable carrier or diluent. Support for this claim can be found in U.S. Provisional patent application No. 60/358,580 incorporated by reference, at, *inter alia*, page 5, lines 11-16, and throughout the specification.

New claim 27 recites the method of claim 1, wherein said chemical modification is a phosphorothioate internucleotide linkage, 2'-O-methyl ribonucleotide, 2'-deoxy-2'-fluoro ribonucleotide, 2'-deoxy ribonucleotide, universal base nucleotide, 5-C-methyl nucleotide, and inverted deoxyabasic modifications. Support for this claim can be found in the U.S. Provisional patent application No. 60/358,580 incorporated by reference, at, *inter alia*, page 15, lines 28-32, and throughout the specification.

Claims 3-8, 10, and 19-24 have been canceled with this amendment without prejudice.

Amendments to the claims are made without prejudice and do not constitute amendments to overcome any prior art or other statutory rejections and are fully supported by the specification as filed. Additionally, these amendments are not an admission regarding the patentability of subject matter of the canceled or amended claims and should not be so construed. Applicant reserves the right

to pursue the subject matter of the previously filed claims in this or in any other appropriate patent application. The amendments add no new matter and applicants respectfully request their entry.

### **The Sequence Listing**

Applicants have enclosed a new sequence listing and request its entry in place of the previously entered sequence listing. The sequence listing adds SEQ ID NO:16208. SEQ ID NO:16208 represents GenBank Accession No. AF100308.1. (*See*, page 54, lines 6-8 in priority application U.S. Ser. No. 60/358,580, which was incorporated by reference). The version of AF100308.1 appearing in the sequence listing as SEQ ID NO:16208 appeared in GenBank on March 11, 1999. The sequence listing adds no new matter and applicants respectfully request its entry.

### **The Restriction Requirement**

The restriction requirement asserts that claims 22, 23, and 24 cover species of linkers that are patentably distinct and thus a species election is required to elect either a vitamin, an antibody, or a hormone linker. Applicants respectfully traverse the species restriction because the claimed species are biologically active molecules conjugated to each strand of a siNA molecule via a common biodegradable linker, yet such molecules can have differing structures themselves. Nevertheless, in the interest of expediting prosecution, claims 22, 23, and 24 have been canceled. As such, the restriction requirement is moot with respect to claims 22, 23, and 24. Additionally, none of the remaining claims recite a linker molecule. Therefore, it is the Applicants' good faith belief that an election to a particular species is not necessary.

The restriction requirement asserts that claims 9-12 and 14-16 cover species of siNA molecules having chemical modifications that are patentably distinct and thus a species election is required to elect either a 2'-O-methyl, 2'-fluoro, 2'-deoxy, or 2'-O-allyl chemical modification. Applicants respectfully traverse the species restriction.

The criteria for a proper restriction requirement between two patentably distinct invention is that (1) the inventions are independent or distinct as claimed **and** (2) there would be a serious burden on the Examiner if the restriction is not required. MPEP §803. A species restriction is proper only if there is a patentable difference between species as claimed **and** there would be a serious burden on the Examiner if the restriction is not required. MPEP §808.01(a). An invention is distinct if (A) the invention as claimed do not overlap in scope, i.e., are mutually exclusive; (B) the inventions as claimed are not obvious variants; and (C) the inventions as claimed are either not capable of use together or can have materially different design, mode of operation, function, or effect. MPEP

§806.05(j). The burden is on the Examiner to provide an example to support the determination that the inventions are distinct. *Id.*

Applicant believes that the species restriction with respect to chemically modified siNA molecules is improper. The siNA molecules are not patentably distinct because the claimed chemical modifications are common structural features of the claimed siNA molecules that can have different chemically modified nucleotides. Thus, siNA molecules having 2'-O-methyl, 2'-fluoro, 2'-deoxy, or 2'-O-allyl nucleotides are molecules that overlap in scope, are variants of one another, and do not have materially different design, mode of operation, function, or effect. Accordingly, siNA molecules having such chemical modifications are not patentably distinct. When related inventions are not patentably distinct as claimed, the restriction is never proper. MPEP §808.02.

Moreover, even if for the sake of argument, siNA molecules having such chemical modifications are considered patentably distinct, Applicants submit that there is no undue burden placed upon the Examiner to search siNA molecules having different chemical modifications because the modifications would not be in a separate classification, would not have separate status in the art, and the search would not involve a different field of search (*e.g.*, would not involve searching different classes/subclasses or employing different search queries). MPEP §808.02. Accordingly, because the inventions are not distinct as claimed and because there would not be a serious burden on the Examiner if the restriction is not required, Applicant believes the species restriction is improper and respectfully requests withdrawal of the restriction requirement.

With respect to the required species election, Applicants elect siNA molecules having 2'-deoxy-2'-fluoro nucleotides. In the event that the claims are held allowable, applicant is entitled to consideration of the additional species that depend from or require the limitation of the allowed claim. The claims readable thereon are claims 1, 2, 9, 11-18 and 25-27.

## **Conclusion**

In view of the foregoing amendments and remarks, the Applicants submit that the claims are in condition for allowance, which is respectfully solicited. If the examiner believes a teleconference will advance prosecution, he is encouraged to contact the undersigned as indicated below.

Respectfully submitted,

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